Zinc for Child Health

Child Health Research Project Special Report
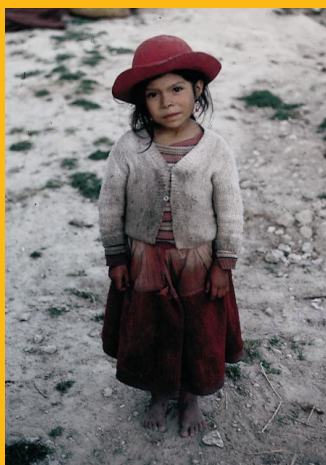
Childhood malnutrition has long been associated with a wide range of adverse outcomes, including an increased risk of morbidity and death from infectious diseases, impaired immunity, and delayed motor and cognitive development. Recent analyses indicate that poor anthropometric status may be the underlying cause of more than half of the childhood deaths in developing countries. When these associations were first noted more than 30 years ago, malnutrition was thought to be due to inadequate dietary protein, or later to insufficient dietary energy intake. Since then, it has been recognized that malnutrition is more complex and usually includes deficiencies of one or more micronutrients. Furthermore, the full consequences of specific micronutrient deficiencies have recently achieved greater recognition. Iodine deficiency in pregnancy causes creatinism and in childhood may be associated with reduced mental performance. Iron deficiency is a well-known cause of anemia, but studies in the last 15 years have also shown an association with mental development and cognitive performance. Vitamin A deficiency has been known to cause xerophthalmia and blindness for many years; however, trials of vitamin A supplementation have unexpectedly demonstrated substantial reductions in child mortality and increased immune responses to childhood vaccines. The recognition of the importance of these three micronutrients has led to interventions to improve their intake in populations likely to be deficient.

Zinc deficiency may be another example of a micronutrient deficiency that is highly prevalent and that has broad, adverse consequences. It is likely that zinc deficiency is widespread in developing countries with particular effects in pregnancy and early childhood. Evidence is accumulating that this deficiency leads to complications of pregnancy and childbirth, lower birth weight and poor growth in childhood, reduced immunocompetence, and increased infectious disease morbidity. Since childhood infectious disease morbidity from diarrhea, pneumonia, and malaria is the cause of most of the childhood deaths in developing countries, it is also plausible that zinc deficiency contributes to the elevated mortality rates still seen in many developing countries.

The Zinc for Child Health meeting was convened to examine the effects of zinc deficiency on child health and development, and to plan additional research to further define the extent of the problem and ways to improve zinc nutriture of populations. Research on iodine, iron, and vitamin A, especially field studies in developing countries, led to well-justified, special attention for these micronutrients in health and nutrition programs. Recent research suggests that zinc also deserves special emphasis. As with the other important micronutrients, a number of program interventions must be available to address the problem in specific settings. Thus, more targeted approaches, such as supplementation and fortification, may have a role, even as efforts are made to improve dietary diversity and quality.

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A conference on Zinc for Child Health was held at the Johns Hopkins School of Public Health in November of 1996 to:

examine research findings and identify research gaps
explore programmatic options for improving zinc nutrition in developing countries

The importance of zinc as an essential trace metal was first shown in 1934 by Todd et al [1]. Follis, Day and McCollum[2] extended these findings and described much of the pathology of severe zinc deficiency, including growth stunting, alopecia, dermatitis, hyperkeratosis and parakeratosis of the esophageal epithelium, and atrophy of germinal and immune tissues. Ten years later Prasad and Halsted[3] suggested zinc deficiency was an underlying cause of stunting and hypogonadism in Iranian farm boys. They subsequently confirmed their hypothesis in Egyptian and Iranian adolescents through studies of zinc metabolism and therapeutic trials[4-9]. Zinc deficiency is now known to occur among children and adults of many countries[10-14], and is thought to be an important public health problem[15,16].

It is well known that zinc is present in many foods, but in most developing countries children have a low intake of foods rich in readily absorbable zinc, such as liver, red meat, poultry, fish, oysters, and crabs[17]. Traditional staple foods, such as cereals, legumes, and tubers, contain zinc, but the presence of phytate, fiber, and lignin reduces its bioavailability. These substances form insoluble complexes with zinc, preventing its absorption[17]. Cow's milk, because of its high concentrations of calcium and casein, and soymilk, because of its phytate content, may further reduce the absorption of zinc from the diet. In contrast, zinc in breast milk is well absorbed. Vegetables and fruits contribute very little to dietary zinc intake, but fruits eaten with cereals may increase the bioavailability of zinc[18].

Zinc metabolism: Implications for assessment of zinc status

Michael Hambidge opened the meeting by explaining that zinc stable isotopes (particularly ^{67}Zinc, ^{68}Zn and ^{70}Zn) can be applied to the identification of populations at risk from zinc deficiency, to provide information on how effectively the intestine is absorbing exogenous dietary zinc and conserving endogenous zinc. They can also yield estimates of the quantity of readily exchangeable zinc in the body, and can provide extensive information on zinc status and the bioavailability of dietary zinc—allowing researchers to relate zinc intake to physiological and pathological conditions. According to Dr. Hambidge, short-term zinc exchange with plasma in a 48-hour period was the most important for zinc dependent metabolic processes, and the most sensitive to dietary zinc restriction—but is extremely difficult to measure outside of the laboratory. He reported that he has had some success measuring zinc plasma enrichment 2-10 days after isotope administration, and extrapolating to estimate short-term exchange. The benefit of this approach is that only a spot urine sample with a rough time estimate is necessary for testing. This method has shown that when dietary zinc is decreased in normal individuals, the exchangeable pool size decreases, and when diet returns to normal, the pool size also returns to normal. In conclusion, he emphasized that the measurement of plasma zinc should be considered along with excretion of endogenous zinc in the feces and urine zinc to give a complete picture of total body zinc status; that stable zinc isotopes provide specific and quantitative information such as fractional total body zinc that is available for metabolic use.

Dr. Hambidge also emphasized that application of these techniques in longitudinal studies provide quantitative data on the effectiveness of prevention programs ranging from simple community measures to reduced dietary phytate to zinc fortification and supplementation programs. Further, judicious application of zinc stable isotope techniques could make a major contribution to progress towards the eradication of zinc deficiency in infants and young children in the developing world.

Assessment of zinc status in children

Due to the dynamic nature of zinc metabolism—plasma zinc turns over 150 times a day in normal individuals, and when zinc is low in the diet, the body reduces the excretion of zinc in order to preserve zinc stores—Janet King stressed the difficulty in identifying zinc deficiency in children. The three basic steps needed to assess zinc status are 1) determining the amount and sources of zinc in the diet; 2) measuring the diet zinc/phytate molar ratio, with a ratio of greater than 15 as an indicator or poor bioavailability, and 3) measuring plasma zinc, with 10.8 μmol/dl as the minimum normal concentration and <9.2 μmol/dl as an indicator for possible deficiency. Although not a validated method, Dr. King mentioned growing support for measuring ^{65}Zn uptake in erythrocytes as an addition to the measurement of plasma zinc.

Zinc status can also be indicated by measuring whether children's growth is affected by zinc supplementation. Factors to keep in mind when measuring zinc status in children are: males are more susceptible to zinc deficiency than females—but respond more readily to supplementation; more zinc supplementation is needed for children on a cereal-based diet, and a large bolus dose may not be as effective as a small daily dose. Finally, measuring zinc status in pregnant women may be an important predictor of low birth weight in their infants. Reduced weight and length at birth may, in turn, predispose the child for continued nutritional deficiency.

Influence of infections on plasma zinc

Studies of the metabolic consequences of experimentally induced infections in human volunteers indicate that these illnesses cause a significant decline in plasma zinc concentrations, according to Kenneth Brown. Likewise, descriptive studies of hospitalized adults with severe infections suggest that plasma zinc concentrations are decreased during the acute phase of illness. These observations imply that the plasma zinc concentration may be less useful as an indicator of zinc status in individuals and populations in low-income countries, where high prevalence rates of infections are common. By contrast with these experimental and clinical findings, three recent community-based assessments of children's plasma zinc concentrations found no association between the presence of infection and plasma zinc levels, possibly because of the reduced severity of infections typically encountered in community settings. Furthermore, the magnitude of other sources of variation in plasma zinc concentration, such as age, recent meals, and time of day, may be greater than the effects of common childhood infections. Available data suggest that the mean plasma zinc concentration may be a useful indicator of population zinc status in developing countries, despite the elevated rates of infection that are frequently observed.

Plasma zinc as a predictor of morbidity in children

Reporting on a study conducted in New Delhi, India, M. K. Bhan found that low plasma zinc concentrations were associated with an increase in diarrheal and respiratory disease morbidity. A cohort of 116 children aged 12-59 months were enrolled in the study while recovering from episodes of acute diarrhea (defined as episodes lasting less than seven days) in an urban slum's community health clinic and followed for three months after recovery from diarrhea. Dr. Bhan found that a child with low initial plasma zinc (non-fasting concentrations < 56 μg/dl) spent significantly greater number of days with watery diarrhea, diarrhea associated with fever and acute lower respiratory infections. The incidence of diarrhea was 47% higher and that of severe diarrhea (defined as greater than five liquid stools per day) was 70% higher in zinc-deficient children.

Assessment of dietary zinc in a population

Rosalind Gibson described an interactive 24-hour recall method developed by her group for assessing zinc and phytate intakes in populations using picture charts, samples of actual foods, food models, and plates to aid respondents in portion size estimation and recall. Food intake data were then used in conjunction with food composition data to calculate nutrient and anti-nutrient intakes in the population. The food composition data were compiled from chemical analysis of composite samples representative of each of the staple foods consumed. High performance liquid chromatography (HPLC) was used to identify and quantify the higher and lower inositol phosphates, and flame atomic absorption spectrophotometry was used for the analysis of zinc in the food samples. Table 1 compares zinc and phytic acid intakes and phytate: zinc molar ratios of children from selected developing countries.

Country	Age (years)	Zinc (mg/day)	Phytic acid (mg/day)	[Phytate]:[Zinc] ratio
Papua New Guinea	6-10	4.4±1.3*	646±663*	12
Ghana	3-6	4.7±1.1	591±153	13
Malawi	4-6	6.6±1.7	1899±590	25
Canada	4-6	6.9±2.3	300**	5
Egypt	1.5-2.5	5.2±1.6	796±249	16
Kenya	1.5-2.5	3.7±0.9	1066±324	28
Mexico	1.5-2.5	5.3±1.3	1666±650	30
Nigeria	1-10	3.6±0.9	-	-
Guatemala	6-8	9.0±2.7	962	11
The Gambia	1.2-1.5	4**	-	-

(* Mean ± SD; **Median)

Table 1. Dietary zinc and phytate intakes of children

Dr. Gibson concluded that probability estimates for risk of zinc deficiency can be calculated from dietary zinc intake alone; however, this would not identify actual individuals in the population who are deficient, or define the severity of the zinc inadequacy. Such information can only be obtained when the dietary intake data are combined with biochemical and functional physiological indices of zinc status. She stressed that this is especially important in developing countries where the coexistence of many other multifaceted health problems often confound the diagnosis of zinc deficiency.

Overview of micronutrient biological interactions

Interactions of Zinc and Other Micronutrients

Carl Keen began this session by stressing that the most important interactions are between zinc and other minerals. For example, several studies now suggest that zinc deficiency can increase the toxicity of lead and to a lesser degree cadmium, and that magnesium competes with zinc for binding sites and when given together can inhibit each other. Dr. Keen also noted that in a state of chronic zinc deficiency, iron stores increase in the tissues and can cause damage via release of oxygen radicals. He therefore suggested the administration of antioxidants along with zinc and other micronutrients in severely malnourished populations. In pregnant rats, copper deficiency can be made more severe by zinc supplementation, and could cause fetal malformation. Dr. Keen closed with comments noting that there exist no data on whether humans have racial and ethnic differences in their need for and ability to metabolize zinc.

Zinc and vitamin A

Evidence of interaction between zinc and vitamin A, and possible health implications of such interaction during deficiency, was explored by Keith West. Zinc is required for synthesis of retinol dehydrogenase, an enzyme that converts retinol to retinaldehyde in the intestine and other tissues, including the retina of eye where this zinc-dependent enzyme participates in the visual cycle. Dr. West noted that zinc may regulate vitamin A absorption and is required for synthesis of retinol-binding protein in the liver. Animal data suggest there may be a threshold for zinc status below which the release and transport of vitamin A from the liver is compromised. Thus, adequate zinc nutriture appears to be necessary for the absorption, transport, storage, and some functions of vitamin A. Conversely, severe vitamin A deficiency may adversely affect zinc absorption through decreased synthesis of an intestinal zinc-binding protein. Dr. West noted that in humans circulating levels of zinc and vitamin A appear to be correlated in malnourished individuals and that, in some hepatic disease states, zinc deficiency could increase risk of night blindness. However, findings from randomized supplementation trials to date have been inconsistent in demonstrating a clear dependence between zinc and vitamin A in affecting nutrient status and health.

Zinc and iron

The interactions between zinc and iron were presented by Paul Whittaker, who noted interactions to be most severe when iron and zinc are given together with zinc in the form of a simple salt. The total amount of iron seems to affect the absorption of zinc and a total dose of iron greater than 25 mg may produce a measurable reduction in zinc absorption. This could occur if iron supplements are taken with a meal, and it has been recommended that iron supplements should be taken between meals. Recent studies using stable isotopes have shown that fortifying foods with iron has no adverse effect on zinc absorption when iron is added at current fortification levels. In reviewing the supplementation of the U.S. diet with zinc and iron, Dr. Whittaker said that there are five zinc salts listed as GRAS (generally recognized as safe) by the FDA for use in food fortification, and from 1970 to 1987, the total poundage of zinc salts used in food continually increased. Twelve iron sources are also listed for fortification of foods with elemental iron being the iron source of choice because it is less expensive to produce and has fewer organoleptic problems. Foods commonly fortified with iron and zinc in the U.S. include flour, bakery goods, cereals, rice, macaroni, and infant formula.

Therapeutic Effects of Zinc on Diarrhea

Summary of studies from Bangladesh [2], India [2], and Indonesia on acute diarrhea

The combined results of studies, most of which have not yet been published, by several investigators examining the therapeutic effects of zinc on acute diarrheal duration and severity were presented by Sunil Sazawal[20-23]. The children in each study were enrolled during treatment for diarrhea in a health facility. Zinc-supplemented children were given zinc with or without other micronutrients. Children not receiving zinc were administered micronutrient mixtures or a placebo. Overall diarrheal duration was decreased by 9% to 23%. In children with a lower initial zinc status, the duration decrease ranged from 22% to 33%. Diarrheal severity as measured by stool frequency or stool output was also reduced in all children by 18% to 39%. In children with lower initial zinc status, diarrheal severity was reduced from 23% to 33%, and in poorer nourished children by 38% to 52%. A meta-analysis of these studies is planned.

Summary of studies from Bangladesh, India, Pakistan, and Peru on persistent diarrhea

Persistent diarrhea is associated with higher morbidity and mortality than severe diarrhea, and also tends to be more prevalent in malnourished populations. The combined results of studies by several investigators examining the therapeutic effects of zinc on persistent diarrheal duration and severity were presented by Mary Penny [22]. As in the acute diarrhea studies, these children were enrolled during treatment for persistent diarrhea in a clinic or community setting. Zinc-supplemented chil-

dren were given zinc with or without other micronutrients. Children not receiving zinc were administered micronutrient mixtures or a placebo. Overall persistent diarrheal duration was decreased 9% to 22%. Although the results were not statistically significant, children with a lower initial zinc status and poorer nourished children had a duration decrease of up to 32%. Diarrheal severity was reduced 21% to 26% in children with lower initial zinc status. Dr. Penny suggested that the results of zinc supplementation on persistent diarrhea may be more spectacular than for acute diarrhea because the children with persistent diarrhea could have more severe malnutrition, other micronutrient deficiencies, or underlying disease states. A meta-analysis of these studies is also planned.

Summary of studies from Bangladesh [3], Brazil, Guatemala, India, Mexico, Papua New Guinea, Peru, and Viet Nam with diarrhea and pneumonia outcomes

D ay two of the symposium opened with a summary of international studies, most of which were recently completed and not yet published, indicating that zinc can prevent diarrhea, acute lower respiratory infections; and pneumonia by Robert Black [23-26]. In India, Bangladesh, and Peru, children were enrolled in the studies after episodes of acute or persistent diarrhea. In the other studies, children were selected from the general community, or were selected because of low birth weight or low weight for age. Children were given zinc with or without other micronutrients; children not receiving zinc were administered micronutrient mixtures or a placebo. Children were supplemented for 2 to 12 weeks and followed for 2 to 12 months. In seven studies providing continuous zinc supplementation, the reduction of diarrhea ranged from 8% to 45%. In three studies providing short-course supplementation (two weeks to two months) with follow-up of two to seven months, two studies found reductions of diarrheal incidence of 38% and 48%, while one study found no difference. In children at least 12 months old, diarrheal incidence decreased 27% to 47%, but there appeared to be less effect in children less than 12 months old. The incidence of acute lower respiratory illness (defined by elevated respiratory rate) or

Preventive Effects of Zinc for Diarrhea, Pneumonia, and Malaria

pneumonia (as defined by elevated respiratory rate coupled with chest indrawing or fever) decreased by 3% to 60%. The reduction was greater in some studies in children with lower initial concentrations of plasma zinc or with poorer nutritional status. A meta-analysis of these studies is also planned.

Table 2. Preventive Effects of Interventions on Incidence of Diarrhea and Pneumonia	Intervention	Diarrhea	Pneumonia
	Water and Sanitation	-27%	None
	Breastfeeding	-10%	-10% to -20%
	Rotavirus Vaccine	-4% for all diarrhea -20% for severe diarrhea	None
	Vitamin A	small for all diarrhea -20%for severe diarrhea	None
	Zinc	-26%	-12%

Dr. Black compared the preventive effects of zinc supplementation with other interventions based on previous reviews of evidence by WHO and the London School of Hygiene and Tropical Medicine (Table 2). The median effects of zinc supplementation on diarrhea and pneumonia are -26% (range -8% to -48%) and -12% (range -3% to -60%), respectively. These effects compare favorably with other interventions.

Effects of zinc on malaria in Papua New Guinea

Anuraj Shankar presented evidence showing that malarial morbidity is reduced by zinc supplementation. Children, aged 6 to 60 months, were matched for malarial parasite density, age, sex, nutritional status, and mosquito net use, and were enrolled in a placebo-controlled community-based study in Wosera, Papua New Guinea. Supplemented children were given 10 mg of zinc, six days a week. After monitoring for 10 months, researchers noted a 29% decrease in overall health center attendance and a 38% decrease in reported fevers. Importantly, blood samples showed that, for children given zinc, there was a 40% reduction in fever associated with *P. falciparum* parasitemia and a 32% reduction in malaria-attributable fever at parasite densities greater than 5000/µl. There was a 36% decrease in fever with parasite densities greater than 50,000/µl (a density representing severe disease). Zinc supplementation had no effect on densities of *P. vivax*—suggesting that zinc may only be useful in reducing specific types of malarial morbidity.

Zinc, Immunity, and Response to Vaccines

Zinc and immune function

The immune system is particularly sensitive to perturbations in zinc status, and zinc deficiency depresses immune competence at fundamental levels, according to Anuraj Shankar. DNA from zinc-deficient animals is more susceptible to digestion by micrococcal nuclease, indicating decreased association of proteins involved in DNA replication and cell division. Dr. Shankar reported that zinc deficiency has deleterious effects on the development and/or function of most immunological cells including T cells, B cells, and macrophages. Reductions in spleen and thymus size were evident in zinc-deficient mice, and production of immunglobulins (IgA, IgM, and IgG) were all decreased. Field studies examining thymic size and DTH in children also indicate decreases in the zinc-deficient state. Macrophage activation and phagocytosis is also compromised in the zinc-deficient animals and humans.

When laboratory animals were deprived of zinc during pregnancy, spleen and thymic size and immune function were reduced in their pups relative to zinc-sufficient controls. Pups born of the zinc-deprived mice continued to show signs of decreased immune function up to 12 weeks after birth—indicating the potential long-term importance of sufficient zinc intake during pregnancy.

Effect of zinc deficiency on immune function

Ananda Prasad, one of the first researchers to study zinc-related stunting in humans in 1961, presented additional evidence suggesting that zinc deficiency interferes with the cell-mediated immune response. In a group of volunteers, Dr. Prasad simulated a mildly zinc-deficient state by administering only 4 to 5 mg (current U.S. RDA = 10 to 15mg/day for adults) of zinc per day in a soy-protein diet. At the end of 8 to 12 weeks, decreased lymphocyte zinc concentration and decreased thymulin activity were observed. When zinc was added to the plasma in vitro, thymulin activity was restored—indicating that the activity of thymulin itself was zinc-dependent.

The researchers also found that interleukin 2 (IL2) production to be greatly reduced in T- helper cells from zinc-deficient donors. Interestingly, the production of IL4, IL5, IL6, and IL10 were unaffected. This implies an imbalance between T-helper 1 cells (TH1) and TH2 cells in zinc deficiency—and may represent an important pathway by which zinc affects cell-mediated immunity. Dr Prasad also noted a decrease in the ratio of CD4/CD8 lymphocytes—indicating a decline in production of naive cells in the thymus. It was also noted that CD8 and CD73 cytotoxic lymphocytes were decreased due to zinc deficiency. In cell culture studies of HUT-78, a T-helper malignant cell line, the S-phase of the cell cycle was inhibited, resulting in decreased mitotic division due to zinc deficiency.

Improvement of immune competence in zinc trials

Results from a trial in India done to evaluate cellular immune competence of children before and after zinc supplementation were presented by Sanju Jalla. The study children, aged 6 to 35 months, were enrolled during treatment for diarrhea in an urban health clinic. Zinc-supplemented children were given zinc with other micronutrients. Children not receiving zinc were given the micronutrient mixtures. Randomly selected children were given a multiple antigen skin test (for response to tetanus, diptheria, streptococcus, tuberculin, candida, trichophyton, and proteus) before and after 120 days of zinc supplementation. The percentage of anergic and hypoergic children, measured by induration

scoring of the skin tests, decreased from 67% to 47% in the zinc supplemented group, but remained unchanged in controls. Analysis of peripheral blood lymphocytes indicated a significant rise in CD3, CD4, and the CD4/CD8 ratio of circulating T-lymphocytes in the zinc group. Thus oral zinc supplementation improved two parameters of immune function.

Zinc and HIV Infection

Zinc deficiency and transmission and progression of HIV infection

Andrea Ruff reported on a trial showing lower plasma zinc concentrations in HIV-positive individuals compared with HIV-negatives. Data from the Multicenter AIDS Cohort Study[27] showed HIV-positive men who progressed to AIDS had mean zinc concentrations of 85.2 µg/dl, while HIV-positive non-progressors had mean zinc of 90.7 µg/dl, and HIV-negative controls had zinc concentrations of 92 µg/dl. Other studies of zinc deficiency and HIV progression in the U.S. and Europe have not shown statistically significant differences.

Based on these results, Dr. Ruff and colleagues enrolled at the time of the birth of their infants, HIV-positive women and sero-negative controls in a trial examining HIV and breastfeeding in Haiti. During the 18-month follow-up, they found that HIV-positive and HIV-negative infants born to HIV-positive mothers didn't grow as well as children unexposed to the virus—based on weight for age scores and height. Sero-negative and sero-positive infants born to infected mothers also had lower CD4 lymphocyte counts than unexposed children. Serum zinc concentrations of these children followed similar patterns. Infected children had the lowest mean concentrations (64 µg/dl), while sero-negatives never exposed to HIV had 73 µg/dl of zinc—HIV-negative infants born to infected mothers had zinc concentrations that fell in between these two means. The mothers of these children also had similar zinc concentrations, with HIV-positive mothers having 71 µg/dl of zinc, and HIV-negative mothers having 78 µg/dl. Although not statistically significant (possibly due to small sample size), Dr. Ruff found that HIV-positive women who transmitted the virus to their children had lower zinc concentrations than non-transmitters.

Effects on Growth, Activity, and Development

Meta-analysis of zinc supplementation effects on growth

A meta-analysis of 25 studies of the effect of zinc supplementation on children's growth was presented by Kenneth Brown. Prospective intervention trials were included in the analysis if they enrolled a concurrent control group and provided suitable data on change in height or weight during the period of observation. The pooled study population amounted to more than 1,000 individuals, with representation of most regions of the world.

The meta-analysis demonstrated that in all children studied, zinc supplementation had a highly statistically significant effect of small magnitude on linear growth and weight gain. Children who were stunted at baseline had a moderately large effect of zinc supplementation on linear growth, while non-stunted children had no effect. With weight gain, the magnitude of the effect of zinc supplementation was inversely related to plasma zinc concentration at baseline.

Effects of zinc supplementation on activity levels of children in India and Guatemala

Evidence for increased child activity levels with zinc supplementation was given by Margaret Bentley, who performed observations with momentary time sampling (instant activity every 10 minutes) in children from India and Guatemala[28-29]. In these two studies, a total of 170 children, 6 to 23 months of age, received supplements for at least one month before study. Zinc gluconate (10 mg of elemental zinc) was given daily to the zinc group.

In India, outcomes were measured as percentages of time spent in each of five activity levels and two groups representing high and low movement and overall rating by two activity scores. Children

in the zinc-supplemented group spent 72% more time performing activities in the high-movement group. Among the zinc-supplemented children, the activity rating by the children's activity rating (CAR) score was 12% higher and by the energy expenditure score was 8.3% higher than in the controls.

Due to the lower age of the infants in Guatemala (ages 6 to 9 months at enrollment), Dr. Bentley used more age-appropriate activity markers to assess their developmental status. After three months, the zinc-supplemented children spent significantly more time sitting than non-supplemented infants, and at 7 months, the zinc group spent 12% more time in play than the placebo group. She stressed that the relationship between the activity increase and locomotor development needs to be investigated, as do the long-term implications of supplementation in terms of developmental status and school performance.

| Table 3. Comparison of Activity Indicators in Zinc-Supplemented and Non-Supplemented Indian Children	Activity indicator	Zinc group (n=48)	Control group (n=48)
	CARRIED ACTIVITY	17.7 ± 10.7*	16.9 ± 12.1
	Stationary 1	48.7 ± 12.0	49.6 ± 14.5
	Stationary 2	6.1 ± 4.0	7.0 ± 4.3
	Slow Movement	16.0 ± 7.3	15.1 ± 10.9
	Moderate Movement	5.4 ± 5.3	3.7 ± 3.8 **
	Fast Movement	2.7 ± 4.0	1.0 ± 1.6 †
	MOVEMENT GROUP		
	Low	70.8 ± 9.0	71.7 ± 10.0
	High	8.1 ± 6.4	4.7 ± 4.4 †
	ACTIVITY RATINGS		
	CAR Score	144.2 ± 30.3	128.7 ± 33.5 †
	Energy Expense	119.5 ± 16.1	110.3 ± 18.9 **

(* Mean ± SD; ** p <0.05; † p <0.01) from Sazawal et al[28]

Potential effects of zinc on child development

Poor nutrition can affect cognitive development through poor growth, increased illness, inhibited central nervous system development, and reduced activity leading to inferior motivation and exploration, according to Maureen Black. Recounting results from trials that examined zinc deficiency and activity and developmental scores, Dr. Black noted that in Egypt, low scores on the Bayley Scales of Infant Development in infants were related to high maternal fiber and phytate intake. In Canada, a study by Friel and colleagues[30] used the Griffiths scale to measure activity, and found greater growth and motor development in zinc- and copper- supplemented children than in age-matched controls (Figure 1). Emphasizing that activity scores are difficult to study because of their close relationship to developmental age, Dr. Black introduced the design of her current study in India examining zinc supplementation and activity, attention, and development. Children are being supplemented for 9 months, and evaluated at 6, 10 and 15 months after enrollment.

Figure 1. Motor Development Among Zinc-Supplemented and Non-Supplemented Infants

from Friel et al.[30]
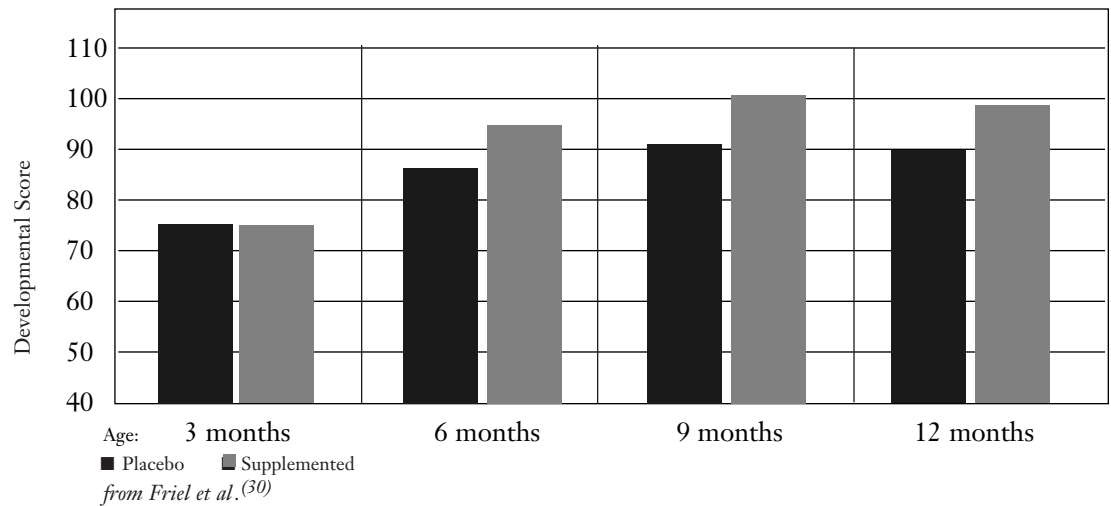
Effects of zinc supplementation on neuromotor and cognitive functions in Chinese children

The session concluded with Harold Sandstead presenting evidence that zinc supplementation improved neuro-psychological functioning and growth in Chinese children. Dr. Sandstead described preliminary findings from a 10-week double-blind controlled trial of zinc repletion in 720 6 to 9-year-old, urban low-income first-graders from Chongqing, Qingdao, and Shanghai, People's Republic of China. Treatments were 20 mg zinc alone, 20 mg zinc with micronutrients, and micronutrients alone. Maximal improvement in neuro-psychological functions occurred after ingesting the zinc-containing mixtures, but not after micronutrients alone. In contrast, maximal growth occurred after the combination of zinc with micronutrients; micronutrients alone had an intermediate effect and zinc alone the least effect. He concluded that zinc deficiency appears to be a problem among poor Chinese children, and zinc repletion will improve their cognition, neuromotor functions, and growth.

Zinc in the Treatment of Diarrhea and Malnutrition

Micronutrient premix for treating malnutrition and persistent diarrhea

Olivier Fontaine of the World Health Organization described the successful development of low-cost, zinc-enriched micronutrient premixes for the treatment of severe malnutrition and persistent diarrhea. Based on guidelines specified by WHO (Table 4)[32, 33], formulae were custom-designed by Nutrisels in Malaunay, France, to be low-cost, easy to manufacture, and easy to use in the field. Factors affecting cost included the choice of mineral salt and amount of the mineral—with lower amounts resulting in higher costs (due to the need for more precise measurement and the greater importance of complete mixing of ingredients). Presentation of the mixture is also important. Researchers decided that powder was better than syrup, tablets, or enrichment of foodstuffs for reasons of both cost and taste of mineral salts, which have to be disguised with flavoring and coloring agents.

Zinc was added in the form of zinc gluconate. Iron was not administered because recent data from WHO show that it is linked with higher mortality in the most severely malnourished children. Therefore, it is contraindicated in the most severely ill children and should only be given after stabi-

lization of nutritional status. Iodine was omitted from the mixtures, because it reacted negatively with copper. Manganese was excluded from the mixture for severe malnutrition for the same reasons. The resulting powder for severe malnutrition was estimated to cost two cents per day.

Preliminary results of studies conducted in refugee camps in Africa indicate that zinc-supplemented micronutrient premixes are both useful and safe for the treatment of severe malnutrition.

	Intake for Severe Malnutrition	Intake for Persistent Diarrhea	Test Mixture for Severe Malnutrition	Test Mixture for Persistent Diarrhea	**Table 4. Intake of Micronutrients**
	(per 100 kcal)	(per day)	(per 100 kcal)	(per 2.3 g)	
Vitamin A	150 µg	400 - 1600 µg	172 µg	1500 µg	
Vitamin D	3 µg	10 - 40 µg	3 µg	10 µg	
Vitamin E	2.2 mg	5 - 20 mg	2.2 mg	15 µg	
Vitamin K	24 µg	15 - 60 µg	4 µg	25 µg	
Vitamin C	10 mg	40 - 160 mg	10 mg	60 mg	
Thiamin (B1)	70 µg	.7 - 2.8 mg	70 µg	1.5 mg	
Riboflavin (B2)	200 µg	.8 - 3.2 mg	200 µg	1.7 mg	
Niacin	1 mg	9 - 36 mg	1 mg	20 mg	
Vitamin B6	70 µg	1 - 4 mg	70 µg	2 mg	
Folic Acid	100 µg	50 - 200 µg	35 µg	400 µg	
Vitamin B12	100 µg	.7 - 2.8 µg	100 µg	6 µg	
Biotin	10 µg	20 - 80 µg	10 µg	30 µg	
Panthotenic Acid	300 µg	3 - 12 mg	300 µg	10 mg	
Potassium	160 mg	—	156 mg	—	
Calcium	80 mg	800 - 3200 mg	93.5 mg	757.5 mg	
Phosphorus	60 mg	800 - 3200 mg	99 mg	125 mg	
Magnesium	10 mg	80 - 320 mg	13.9 mg	106 mg	
Iron	—	—	—	—	
Zinc	2 mg	10 - 40 mg	2.25 mg	15.2 mg	
Copper	.3 mg	1 - 4 mg	.29 mg	2 mg	
Iodine	12 µg	70 - 280 µg	—	—	
Selenium	4.7 µg	20 - 80 µg	—	—	
Manganese	300 µg	1.25 - 6.00mg	—	3.96 mg	

Possibilities for treatment of acute diarrhea

George Fuchs said that there is evidence in favor of using zinc supplementation to treat cases of acute diarrhea. An increasing amount of data demonstrating benefit continues to emerge from epidemiologic and clinical trials. A short course of zinc is feasible from a cost perspective and the routine use of zinc, at least as a short course, appears to be practical for all children with severe diarrhea. Operational questions remain, however, including the dosing regimen (single or multiple daily dose, or a dose several times per week) and whether or not zinc should be administered as a separate supplement, as part of a micronutrient mix, or with meals. Awaiting this information should not prevent the use of zinc for treatment of acute diarrhea. Additional answers are needed concerning zinc toxicity, and its interactions with other micronutrients—especially copper. Any remaining doubts about safety need to be quickly addressed.

Dr. Fuchs noted that if zinc is to be ultimately incorporated into diarrheal disease programs, it will need to be included as part of an overall package of actions: ORS, general nutritional therapy, advice on appropriate feeding and breastfeeding, and sanitation (handwashing and proper disposal of excrement). He concluded that the evidence to include zinc in programs is nearly sufficient, and could be compelling, provided the answers to a few questions become available.

Program Options to Prevent Zinc Deficiency

Dietary interventions

A dietary modification program designed to increase the zinc, vitamin A, and iron content, and bioavailability of diets in rural southern Malawi, was described by Rosalind Gibson. The Tulimbe nutrition project consisted of three aspects: 1) increase intake of foods with a high content and bioavailability of zinc; 2) increase intakes of foods known to enhance zinc absorption, and 3) use soaking, germination, and/or fermentation to induce phytase hydrolysis of phytic acid.

In this project, Dr. Gibson encouraged dietary diversification through the consumption of zinc-rich fish caught in Lake Malawi and sold fresh or dried in local markets in the area around the project, as well as the consumption of boiled, ground nuts as snacks. The addition of ground nut flour to maize-based porridges and nsima is also recommended to enhance the zinc as well as energy, fat, and iron densities of the rural diets. She also emphasized the enhancing effect of certain amino acids and organic acids (e.g., citric, lactic, butyric, formic acid) on zinc absorption. When released during the digestion of cellular animal proteins and when formed during fermentation, these substances enhance zinc absorption, possibly by forming soluble ligands with zinc and/or by forming complexes with zinc, thereby preventing the formation of the insoluble zinc-phytate complex. Dr. Gibson concluded by saying that dietary modifications to increase the bioavailability of zinc do not jeopardize dietary adequacy and may enhance the intake and bioavailability of other nutrients concomitantly (e.g., iron and calcium). The advantages of food-based interventions are that they avoid the antagonistic interactions among zinc and other micronutrients, are community-based, and may be culturally acceptable and sustainable.

Plant breeding strategies

Improved plant breeding strategies to boost dietary intake of bioavailable zinc were outlined by Marie Ruel. The three most promising plant breeding strategies to achieve this goal are: 1) increasing the concentration of zinc in the plant; 2) reducing the amount of phytic acid, and 3) raising the levels of sulfur-containing amino acids (methionine, lysine, and cysteine), which are thought to promote zinc absorption.

Breeding zinc-efficient staple crops, i.e., plants that are better adapted and yield more in zinc-deficient soils, is both agronomically feasible and desirable, and may increase the zinc intake of poor populations whose diets rely mainly on staple crops. Reducing the concentration of phytic acid

Table 5. Effects of Increasing Zinc Density in Mature Pea Seed or Whole Wheat Grain on Zinc Bioavailability	Meal	Zinc density (mg/kg)	Phytic acid (%)	Bioavailability (%)	Zinc absorbed (mg)
	Pea (low zinc)	9.0	1.23	77.4	5.3
	Pea (high zinc)	47.8	1.16	74.9	24.6
	Wheat (low zinc)	8.8	1.17	57.4	5.9
	Wheat (high zinc)	33.0	1.18	56.1	18.7

(Data from Welch et al.[34] and House and Welch.[35])

(a strong inhibitor) and/or raising the level of sulfur-containing amino acids (promoters) could have the additional benefit of increasing the bioavailability of zinc and possibly of other trace minerals also present in the plant.

The key issues, according to Dr. Ruel, are not those of cost, or whether plant breeders eventually will be successful in developing plants that provide more bioavailable zinc. Rather, the two key issues are: 1) whether the agronomic advantages of the zinc-dense plants are sufficiently great that national breeding programs will want to incorporate these characteristics into their lines of staple food crops so that they will be widely adopted by farmers, and 2) whether the additional zinc contained in the plants will be of sufficient magnitude and bioavailability so as to have an appreciable impact on the zinc status of vulnerable populations.

Micronutrient supplements for children

Lindsay Allen began her presentation by noting that in populations with severe malnutrition or high morbidity, food-based dietary interventions are probably not adequate to restore nutritional status, and micronutrient supplements are required. She reported the results of a recent longitudinal study in which the intake of absorbable zinc was calculated to be inadequate in 27% of a group of preschoolers in Egypt, 73% in Mexico, and 97% in Kenya. Zinc intake is also likely to be inadequate during the period from about 6 months to 2 years of age when infants are consuming some breast milk and some solid foods. If only small quantities of zinc-rich foods are given at this time, providing zinc supplements to infants should be a programmatic priority.

Dr. Allen said that it may be practical and cost-effective to add zinc to iron or multivitamin supplements that are now provided by UNICEF and other organizations. Questions that need to be answered prior to initiating supplementation programs are clarifications of the best type of zinc salt to use in supplements (absorbability of zinc differs with type of zinc salt and with increasing stomach pH); the dose of zinc required (e.g., 5 mg/day, or 10 mg/day), and the frequency with which it must be given. It is not known, for example, whether doses given once or twice a week are effective or whether consistent daily doses are required. She concluded that because of the apparent benefits of zinc for child health, it is critical that methods of supplementation be developed as soon as possible.

Supplementation in pregnancy

The consequences of severe maternal zinc deficiency, including inability to conceive, high risk of spontaneous abortions, neural tube defects, and anencephaly, were reviewed by Laura Caulfield. Zinc is also necessary for estrogen-dependent functions such as expulsion of the placenta and coordination of uterine muscles during birth, and mild-to-moderate zinc deficiency during pregnancy has been shown to increase problems during parturition. Women with low plasma zinc concentrations were

also shown to have a three to seven times increase in premature rupture of fetal membranes, three times higher incidence of placental abruptions, and a two to nine times higher prevalence of prolonged labor or protracted second stage labor than women with normal zinc. In reviewing Goldenberg's zinc supplementation trial in Alabama[36], Dr. Caulfield noted longer gestation time and 25% to 50% reduction of pre-term delivery in the zinc-supplemented women.

Dr. Caulfield ended her discussion of zinc supplementation in pregnancy by reviewing the designs from current randomized, prospective trials for zinc supplementation in Guatemala, Chile, Peru, Ecuador, Bangladesh, and Indonesia. She also emphasized the need for zinc and iron interactions to be clarified prior to the initiation of supplementation programs.

Supplementation of lactating women

The effects of a zinc supplement on maternal zinc status and milk zinc concentrations were reviewed by Nancy Krebs, who said that the maternal demand for zinc is highest in the first four months of lactation. In her study of 71 well-nourished, lactating women in Denver, women received either a daily 15 mg zinc supplement or placebo. Overall mean zinc intakes were 13.0 mg/d for the non-supplemented group and 25.7 mg/d (including supplement) for the supplemented group. The high initial concentrations of breast milk zinc (average of 2.5 mg/day) decreased after six months, regardless of zinc supplementation status or plasma zinc concentration, although supplemented women showed a slower decline. This indicates that women at or near RDA zinc intakes will not transfer further zinc to their breast milk.

Studies from the developing world are few, and tend to show breast milk zinc concentrations below, but still similar to, those of well-nourished women in the United States. One possible reason for this, according to Dr. Krebs, is that post-partum, zinc could be released from a woman's bones to boost the lactation output. Another reason for the surprising concentrations of breast milk-zinc in the developing world could be poor study design. Dr. Krebs ended her talk by calling for further longitudinal studies on the topic using well-timed sampling and large enough sample sizes to correct for high within-individual variation.

Fortification

Benefits of fortification were discussed by Peter Ranum, who said that zinc is used in two blended products, corn-soy blend and wheat-soy blend, provided under the U.S. Food for Peace program, where only 9 parts per million are added. This has recently been recognized as being too low and efforts are under way to increase the level. None of the other fortified Food for Peace commodities, such as wheat flour, are fortified with zinc. Mr. Ranum reported that the three types of zinc salts best for fortification are zinc sulfate, zinc oxide, and zinc gluconate. They are all white powders with good bioavailability and little effect on the shelf life or appearance of the food. Zinc oxide is the cheapest, partly because it contains 80% zinc compared to 36% in zinc sulfate. The cost of zinc from the sulfate is 6 times that from the oxide, while the gluconate costs 18 times more than the oxide. Zinc oxide is the most commonly used form of zinc in fortification of cereals, with the sulfate next and the gluconate used very infrequently.

He added that the level of a nutrient to add to foods such as wheat flour may often be based on restoration levels or adding enough of the nutrient to flour to bring the level back to what was in the wheat. The Food and Nutrition Board of the National Academy of Sciences proposed in 1974 that this be done for all milled cereals (flour, rice, and corn) suggesting a level of 22 parts per million zinc along with nine other nutrients. While the proposal received considerable attention, it was never enacted. Some bakers did offer specially fortified breads with the proposed fortification including zinc, but there was low consumer interest in such fortified bread, so they eventually disappeared from the market. In conclusion, zinc could be included in the cereal enrichment standards, if there was a demonstrated need for more zinc in the general diet.

Moving from science to programs

Alfred Sommer concluded that moving from science to programs requires that some person or group of individuals, particularly scientists originally involved in the discovery, take an active, balanced, objective leadership role. Dr. Sommer emphasized several steps to developing successful programs: making the discovery; "proving," to one's own satisfaction, that the discovery is indeed real; documenting variability of the results in different populations, environments, and cultures; overcoming the traditional reticence of other scientists in the field and convincing them of the discovery's validity; educating policy makers about the discovery and its implications; and devising and establishing programs that actively put the discovery to work. Especially important are mechanisms for sharing information and disseminating results, bringing the scientific discussion to closure, and involving a network of organizations, particularly credible entities like UNICEF and WHO. Nothing can substitute for a dedicated funding agency, regardless of the support that others might bring to the table.

Dr. Sommer said that crucial to program success is spreading the word. When moving from science to programs with vitamin A, he placed stories, either early "warnings" of a potential breakthrough or subsequent ones, after confirmation of the findings. These in turn stimulated other media outlets that drew further political and financial support. In the U.S., a TV story also captured the attention of members of Congress, which increased its support for vitamin A and child survival research.

Summary of program options

According to David Alnwick, who summarized the meeting's conclusions, zinc can improve the treatment of severe malnutrition, and acute and persistent diarrhea. The main benefits for child health and growth may be obtained, however, by ensuring that all children received adequate intakes of zinc. There are a range of approaches to improve zinc deficiency, which programs need to consider, such as dietary, improvement, plant breeding to increase zinc content, the use of zinc supplements for children and pregnant and lactating women, and food fortification. He emphasized that it is possible to change micronutrient intake of millions of people in a short period of time. In the last five years for example, in the world as a whole, about 60% of the salt consumed by people has been iodized, and about 30% of the world's young children who are at risk of vitamin A deficiency receive regular vitamin A supplements. Iron supplementation and general food fortification programs, are however, only just beginning, and further work is necessary to extend benefits of these more widely. There was now ample evidence that zinc supplementation improved recovery of children suffering from severe malnutrition. International organizations should formulate and disseminate guidelines on the use of zinc in the treatment of severe malnutrition, support the training of health providers, and ensure adequate supplies of zinc and other micronutrients.

The meeting provided ample evidence that efforts to improve dietary intake of zinc would reduce diarrheal morbidity and improve child health in areas where zinc intakes were sub-optimal. Dietary interventions tailored to fit at-risk populations have been shown to be effective in reducing zinc deficiency and its related morbidities, and should be implemented. The feasibility of prevenative supplementation and fortification programs should be considered, and further work on plant breeding to develop staple foods with a higher content of bioavailable zinc is needed. Work to determine the practicality and effectiveness, on a large scale, of routine supplementation with zinc of children over 6 months of age should be a priority. The meeting heard very little evidence for any harm from regular low doses of zinc, given in physiological amounts, but plenty of evidence that such intervention might reduce morbidity and presumably mortality. Potentially reducing malarial morbidity by 30% would be of enormous benefit. Urgent work was also needed to further clarify the potential of zinc supplementation in pregnancy on reducing delivery complications and low birthweight. In many developing countries, where maternal mortality rates are up to 100 times higher than those in industrialized countries, the role of micronutrient supplementation in helping to bring these appallingly high rates down needs to be urgently evaluated. He concluded his summary by calling

for further research on the effects of zinc. Important questions that need to be answered before large-scale programs are implemented appeared to be the interaction of zinc and other micronutrients, particularly iron and copper, and ways in which additional zinc could be delivered to large populations. The costs of good population-based research which is needed to fully quantify the benefits of improving zinc status may be substantial, but this would be a small price to pay if the consequences of marginal zinc deficiency are as profound as many of the studies summarized at this meeting indicate.

Research Priorities

Malnutrition in developing country children is thought to be the underlying cause of at least half of the deaths and a substantial portion of the infectious disease morbidity. In recent years deficiencies of specific nutrients have been recognized to be responsible in part for this excess burden of disease. For example, supplementation with vitamin A reduces child mortality and has been considered one of the most cost-effective health interventions for increasing disability adjusted life years in developing countries. Recent research, summarized here, suggests that zinc may be another specific nutrient for which there is widespread deficiency and great benefit of supplementation or other approaches to improve zinc nutriture.

Recent studies have demonstrated that zinc supplementation has both therapeutic and preventive benefits in regard to childhood infectious diseases. Zinc supplementation has been shown to reduce the duration and severity of diarrhea and to reduce the occurrence of diarrhea, respiratory infections, including pneumonia, and malaria, while improving immunocompetence. These studies in developing countries also indicate that with zinc supplementation, growth is improved, as are motor and cognitive aspects of child development.

Further work is urgently needed to understand:

• The prevalence of zinc deficiency and the related disease burden, including validation of zinc-deficiency indicators.

• The effects of zinc supplementation on child health, starting with a meta-analysis of prevention effects; trials examining infectious disease morbidity, especially on pneumonia and malaria, in Africa and Asia; studies on improvements in child growth and development; research on immune response to childhood vaccines; effects on child mortality; and long-term safety trials.

• The therapeutic effects of zinc on acute and persistent diarrhea, including a meta-analysis of therapeutic outcomes, and the effectiveness of zinc therapy for treatment of diarrhea in programs, as well as for improvement in zinc status and prevention of subsequent morbidity.

• The effects of zinc supplementation during pregnancy on child health, including a meta-analysis of the effects of supplementation in pregnancy on child health outcomes; immune response to childhood vaccines; and studies of the effects on vertical transmission of HIV.

• Delivery issues related to improving zinc nutriture, focusing on which is the best zinc salt; zinc's interactions with other micronutrients; the effects of dietary phytates and fiber on zinc bioavailability; necessary dosages, and the feasibility of zinc supplementation versus increasing available dietary zinc; and the best strategies for zinc fortification of staple foods.

Acknowledgments

References

1. Todd WR, Elvehjem CA, Hart EB. Zinc in the nutrition of the rat. *American Journal of Physiology* 1934; 107:146-56.

2. Follis RJ, Day H, McCollum E. Histological studies of the tissues of rats fed a diet extremely low in zinc. *Journal of Nutrition* 1941; 22:223-37.

3. Prasad AS, Halsted JA, Nadimi M. Syndrome of iron deficiency anemia, hepatosplenomegaly, hypogonadism, dwarfism and geophagia. *American Journal of Medicine* 1961; 31:532-46.

4. Prasad A, Miale Jr A, Farid Z, Sandstead H, Schulert A. Zinc metabolism in patients with syndrome of iron deficiency anemia, hepatosplenomegaly, dwarfism and hypogonadism. *Journal of Laboratory and Clinical Medicine* 1963; 61:537-49.

5. Prasad AS, Miale Jr A, Farid Z, Sandstead HH, Schulert AR, Darby WJ. Biochemical studies on dwarfism, hypogonadism and anemia. *Archives of Internal Medicine* 1963; 111:407-28

6. Sandstead HH, Prasad AS, Schulert AR, Miale AJ, Bassily S, Darby W. Human zinc deficiency, endocrine manifestations, and response to treatment. *American Journal of Clinical Nutrition* 1967; 20:422-42.

7. Halsted J. Human zinc deficiency. *Transactions of the American Clinical Climatological Association* 1970; 82:170-6.

8. Halsted J, Ronaghy H, Abadi P, Haghshenass M, Amerhakemi GH, Barakat RM, Reinhold JG. Zinc deficiency in man: The Shiraz experiment. *American Journal of Medicine* 1972; 53:277-84.

9. Halsted J. Events surrounding the original demonstrations of human zinc deficiency. *Progress in Clinical Biological Research* 1977; 14:1-9.

10. Ronaghy H, Reinhold J, Mahloudji M, Ghavami P, Fox M, Halsted J. Zinc supplementation of malnourished schoolboys in Iran: increased growth and other effects. *American Journal of Clinical Nutrition* 1974; 27:112-21.

11. Ronaghy H, Halsted J. Zinc deficiency occurring in females. Report of two cases. *American Journal of Clinical Nutrition* 1975; 28:831-6.

12. Sandstead HH. Zinc in human nutrition. In: Bronner F, Coburn J, eds. *Disorders of Mineral Metabolism*; vol 2. New York: Academic Press, 1981:93-157.

13. Hambidge K, Casey C, Krebs N. Zinc. In: Mertz W, ed. Trace *Elements in Human and Nutrition*; vol 2. 5th ed. New York: Academic Press Inc., 1986:1-137.

14. Gibson R. Zinc nutrition in developing countries. *Nutrition Research Review* 1994; 7:151-73.

15. Sandstead HH. Zinc deficiency: A public health problem. *American Journal of Diseases in Childhood* 1991; 145:835-59.

16. Sandstead HH. Is zinc deficiency is a public health problem? *Nutrition* 1995; 11:87-92

17. Walsh CT, Sandstead HH, Prasad AS, Newberne PM, Fraker PJ. Zinc: Health effects and research priorities for the 1990's. *Environmental Health Perspectives* 1994; 102:Supp 2:5-46.

18. Bell JG, Keen CL, Lonnerddal B. Effect of infant cereals on zinc and copper absorption during weaning. *American Journal of Diseases in Childhood* 1987; 141:1128-32.

19. Sachdev HPS, Mittal SK, and Yadav HS. A controlled trial on utility of oral zinc supplementation in acute dehydrating diarrhea in infants. *Journal of Pediatric Gastroenterology and Nutrition* 1988; 7: 877-81.

20. Sazawal S, Black RE, Bahn MK, Bhandari N, Sinha A, Jalla S. Zinc supplementation in young children with acute diarrhea in India. *New England Journal of Medicine* 1995; 333: 839-844.

21. Tomkins A, Behrens R, Roy S. Symposium on "Functional significance of micronutrient undernutrition." *Proceedings of the Nutrition Society* 1993; 52, 131-142.

22. Sachdev HPS, Mittal NK, Yadav HS. Oral zinc supplementation in persistent diarrhea in infants. *Annals of Tropical Diseases* 1990; 10: 63-69.

23. Sazawal S, Black RE, Bhan MK, Jalla S, Bhandari N, Sinha A, Majmudar S. Zinc supplementation reduces the incidence of persistent diarrhea and dysentery among low socioeconomic children in India. *Journal of Nutrition* 1996; 126: 443-450.

24. Nihn NX, Thissen JP, Collette L, Gerard G, Khoi HH, Ketelslegers JM. Zinc supplementation increases growth and circulating insulin-like growth factor (IGF-1) in growth retarded Vietnamese children. *American Journal of Clinical Nutrition* 1996; 63: 514-519.

25. Rosado JL, Lopez P, Munoz E, Martinez H, Allen LH. Zinc supplementation reduced morbidity, but neither zinc nor iron supplementation affected growth or body composition of Mexican preschoolers. *American Journal of Clinical Nutrition* 1997; 65: 13-19.

26. Sazawal S, Black R, Bhan MK, Jalla S, Sinha A, Bhandari N. Efficacy of zinc supplementation in reducing the incidence and prevalence of acute diarrhea—A community-based, double-blind, controlled trial. *American Journal of Clinical Nutrition* (in press).

27. Tang AM, Graham NM, Kirby AJ, McCall LD, Willett WC, Saah AJ. Dietary micronutrient intake and risk of progression to acquired immunodeficiency syndrome (AIDS) in human immunodeficiency virus type 1 (HIV-1)-infected homosexual men. *American Journal of Epidemiology* 1993; 138(11): 937-51.

28. Sazawal S, Bentley M, Black RE, Dhingra P, George S, Bhan MK. Effect of zinc supplementation on observed activity in low socioeconomic Indian preschool children. *Pediatrics* 1996; 98: 6 1132-1137.

29. Bentley ME, Caulfield LE, Ram M, Santizo MC, Hurtado E, Rivera JA, Ruel MT, Brown KH. Zinc supplementation and activity patterns of rural Guatemalan infants. *Journal of Nutrition* (in press).

30. Friel JK, Andrews WL, Matthew JD, Long DR, Cornel AM, Cox M, McKim E, Zerbe GO. Zinc supplementation in very-low-birth-weight infants. *Journal of Pediatric Gastroenterology & Nutrition* 1993; 17(1):97-104.

31. Penland JG, Sandstead HH, Alcock NW, Dayal HH, Chen XC, Li JS, Zho F, Yang JJ. Preliminary Report: Effects of zinc and micronutrient repletion in growth and neurological function of urban Chinese children. *Journal of the American College of Nutrition* (in press).

32. World Health Organization. Management of severe malnutrition— A manual for physicians and other senior health workers. WHO, Geneva. 1977.

33. International Study Group on Persistent Diarrhea. Evaluation of an algorithm for the treatment of diarrhea: A multicentre study. *Bulletin of the World Health Organization* 1996; 74 (5): 479-488

34. Welch RM. House WA. Allaway WH. Availability of zinc from pea seeds to rats. *Journal of Nutrition* 1974; 104(6): 733-740.

35. House WA, Welch RM. Bioavailability of and interactions between zinc and selenium in rats fed wheat grain intrinsically labeled with ^{65}Zn and ^{75}Se. *Journal of Nutrition* 1989; 119:916-21.

36. Goldenberg RL., Tamura T., Neggers Y., Copper RL., Johnston KE., DuBard MB., Hauth JC. The Effect of zinc Ssupplementation on pregnancy outcome. *Journal of the American Medical Association* 1995; 274 (6): 463-8.

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